4. INTRODUCTION

4.1 Investigational Plan

Vical Inc. proposes to administer the immunotherapeutic Allovectin-7 intratumorally to melanoma patients who are classified with Stage III locoregional disease, in-transit metastasis, or nodal disease; or Stage IV metastatic disease in skin, subcutaneous tissue, lymph node(s) and/or lung to assess safety and efficacy. Patients selected to participate will have at least one unresectable metastasis and have relapsed from or have not responded to front-line chemotherapy **or biotherapy**. This immunotherapeutic approach is intended to stimulate an immune response by expressing HLA-B7 antigen within the tumor and potentially restoring some degree of major histocompatibility complex (MHC) class I tumor antigen presentation.

4.2 Overview

The management of malignant melanoma remains unsatisfactory. Even with generous surgical margins and regional lymphadenectomy, many **tumors** will recur (1,2).

Treatment modalities for patients with systemic metastases are dependent on sites of metastases. Options include radiation, or surgery as an effective palliative treatment for isolated metastases where indicated according to patients' life expectancy and course of disease. A number of chemotherapeutic regimens have been evaluated; dimethyl triazeno imidazole carboxamide (DTIC) is the best, single chemotherapy agent with a response rate in systemic, metastatic disease of about 20% (3). Significantly increased response rates can be expected with newer combination programs such as tamoxifen, BCNU, cis-platinum and DTIC (4), but this is at the cost of increased toxicity. There is no consensus on second line treatment, and no treatment after front-line therapy for Stage III and IV disease has been shown to be effective. At this point, consideration often is given to the use of cytokines or other experimental approaches.

Systemic immunotherapy with cytokines including interleukin-2 and α-interferon in metastatic melanoma has been the subject of extensive investigation, as have biochemotherapy regimens involving chemotherapy plus immunomodulatory agents such as BCG or levamisole, or chemotherapy plus cytokines. High dose interferon α can reduce recurrence in Stage I and II melanoma by about 40%, but it is associated with significant toxicity (5). There is continuing effort to identify other immunotherapies that might lend themselves to adjuvant use.

The role of the immune system in malignant melanoma remains an area of intense interest. Melanoma antigens have been well studied in the past, as has evidence of a host immune response (4-7). Agents that can stimulate non-HLA-restricted cellular cytotoxicity, such as interferons and interleukin-2, have produced sustained regressions in some patients (8). The toxic side effects of these agents, however, are considerable,

with several deaths associated with the use of high dose regimens.

It is now possible to trigger an immune response through gene transfer. Numerous models have been developed which have led to several clinical trials exploring the possibility of manipulating either tumor cells or host lymphocytes transfected with a variety of cytokine genes (9). Other specific gene therapy strategies have sought to influence directly the interaction between immunocyte and antigen presenting cell by enhancement of HLA-restricted immunity.

5. BACKGROUND AND RATIONALE

5.1 Allovectin-7

Allovectin-7 is a direct gene therapy product developed by Vical Inc. which contains the gene for the highly immunogenic MHC class I transplantation antigen, HLA-B7. It is administered by direct intratumoral injection. The product contains plasmid DNA, VCL-1005, which encodes the HLA-B7 heavy chain and β2 microglobulin proteins. The β2 microglobulin allows synthesis and expression of the complete MHC complex on the cell surface (10). The plasmid is complexed with the cationic lipid mixture, DMRIE/DOPE (2,3-bis(tetradecyloxy)propyl,2-hydroxyethyl, dimethylammoniumbromide/dioleoyl phosphatidylethanolamine), which facilitates transfection of the plasmid DNA. Qualitative or quantitative changes in MHC class I antigens on the tumor cell regulate the sensitivity of the tumor to immunological rejection by autologous T lymphocytes (1). In experimental tumor models (11-13), variation in the expression of MHC class I antigens has been shown to exert a decisive influence on local tumor growth and metastases. Total or selective loss of MHC class I antigens have been reported in 10%-30% of biopsies of human melanoma **tumors** (14). In some cases, a correlation was found between HLA loss and poor prognosis (15).